REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 93, 99, 100, 104, 106, 107, 116, 121 and 122 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 121 and 122 have been rejected under 35 U.S.C. §112, first paragraph, as lacking written description for the term "kit". This rejection is obviated by the amendment to claims 121 and 122 to replace "kit" with "system", without prejudice. Support for the term "system" with the features recited in claims 121 and 122 is found in Example 8, pages 53-54 of the present specification (see in particular line 10 on page 54 for the term "system").

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 93, 99, 100, 104, 106, 107 and 116 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Nakamura et al., *Infect. Immun.* 61:64-70 (1993), and further in view of A. Campbell, Laboratory Techniques in Biochemistry and Molecular Biology, Volume 13, Chapter 1, pages 1-33, 1984. This rejection is respectfully traversed.

Before addressing the specifics of this rejection, the examiner's comments relating to Dr. Okamura's declaration are addressed first because they are relevant to the rejection and because Dr. Okamura's declaration should be carefully taken into account for evaluating the unobviousness of the presently claimed invention.

Regarding the examiner's specific comments on the 1.132 declaration of Dr. Okamura, it appears that the examiner is giving little weight to this declaration, stating that it is largely only opinion/conclusion. However, applicants submit that more weight should be given to Dr. Okamura's declaration because Dr. Okamura, who is a co-author of both the cited and applied Nakamura reference and the latter published Okamura reference used by the examiner as evidence, provides insight into what the authors of these references were thinking at that time. Dr. Okamura reveals at page 6, lines 9-19 of the declaration the following important fact which was not disclosed by the Nakamura reference published before the filing date of the instant application:

> I and my co-inventors in the present invention consistently and diligently continued studying the factor of Nakamura et al. and, prior to the publication of Okamura et al., we found that mouse liver cells produce a mouse interleukin-18 (mIL-18) corresponding to the IGIF in Okamura et al.

> (hereinafter designated as "mIL-18/IGIF") and serve as a cell source for mIL-18/IGIF and we established a technique for producing sufficient amounts of mIL-18/IGIF necessary for preparing the monoclonal antibody of the instant application using recombinant DNA technology with mRNA isolated from mouse liver cells as mIL-18/IGIF-producing cells.

Thus, as described above, the present inventors finally found and identified the cells which are capable of producing mouse IL-18/IGIF consisting of the amino acid sequence of SEQ ID NO:2, a finding which was neither disclosed nor suggested by Nakamura. The present inventors further succeeded in obtaining mouse IL-18/IGIF, using mRNA isolated from these cells and recombinant DNA techniques, in an amount sufficient for preparing monoclonal antibodies against mouse IL-18/IGIF.

Dr. Okamura further stated in the passage extending from page 6, line 20 to page 7, line 3 of his declaration:

> I declare that the above finding was the breakthrough or the key to success for obtaining the monoclonal antibody of the instant application and this is evidenced by the disclosure of Okamura et al., at page 3972, left column, lines 12 to 15:
>
> The complementary DNA for the IGIF has recently been cloned (unpublished data). This will enable a sufficient supply of recombinant IGIF or the antibody against it for examination of its biological actions.

It should be pointed out that the "above finding" was "the key to success for obtaining the monoclonal antibody of the instant application." In other words, the monoclonal antibody of the present invention would not have been obtained without the finding.

> With regard to the examiner's comment that:
>
> contrary to applicants argument that in Nakamura et al., the authors were unable to obtain the factor in an isolated and purified form, Nakamura teaches the purification of the factor (title) by different procedure such as ammonium sulfate precipitation, DEAE-sepharose column, ultrogel, phenyl-sepharose column (page 66, 1st column, Figure 1, and Table 1), and gel electrophoresis (page 66, 2nd column, and page 67, Figure 2),

applicants respectfully submit that, although Nakamura discloses a purification method for Nakamura's factor using ammonium sulfate precipitation, DEAE-sepharose column, ultrogel, phenyl-sepharose column, and gel electrophoresis in this order, Nakamura actually failed to purify and isolate Nakamura's factor. In fact, Nakamura states at page 68, 2nd column, lines 25-28:

> Since the factor lost its activity in SDS-PAGE, we also failed to definitely establish that the band revealed by SDS-PAGE was the factor.

Therefore, Nakamura cannot be considered to disclose any method for successfully purifying and isolating Nakamura's factor.

The examiner has also cited Timmann et al. (*J. Immunol.* 1991, 146(4):1265-70) to show that identifying a cell source producing a serum protein was not the only way for producing sufficient amounts of serum proteins.

Timmann, however, discloses a purification method which was applied to a substance called "Factor H", which is present in human serum in quite a high concentration of about 40mg/l (see "Abstract" and page 1268, first column, lines 20-22). Furthermore, Timmann uses 1.9 liters of human serum, which contains about 40 mg of "Factor H" per liter and would therefore be equivalent to about 76 mg of "Factor H". In addition, Timmann identified human liver cells as the cells that produce "Factor H", and determined the base sequence encoding "Factor H" on the basis of a mRNA isolated from the liver cells. "Factor H" was then prepared by recombinant DNA techniques in light of the determined base sequence.

By contrast, as shown in Table III at page 2539 of Joshi et al., *Journal of Immunology*, 169:2536-2544 (2002), a copy of which is attached hereto, mouse serum contains only about 2,500 to 5,000 pg/ml of mouse IL-18/IGIF even when LPS is injected as an inducing agent of mouse IL-18/IGIF production. 2,500 to 5,000 pg/ml is equivalent to 0.0025 to 0.0050 mg/liter, which is quite a low concentration relative to 40 mg/liter of

"Factor H" in human serum. It should furthermore be noted that a mouse having about 30g body weight possesses only about 1.5 ml of blood. So, even if mouse blood is taken to consist of 100% serum, nearly 10,000,000 to 20,000,000 mice would be needed to prepare the same amount (76 mg) of mouse IL-18/IGIF as that of "Factor H" used in Timmann. As would be appreciated by those of ordinary skill in the art, it would be almost impossible to collect serum from about 10,000,000 to 20,000,000 mice. Therefore, applicants believe that the method disclosed by Timmann and referred to by the examiner is not applicable to mouse IL-18/IGIF.

In addition, applicants believe that Timmann were successful in determining the base sequence encoding "Factor H" because they were already aware that human liver cells are the source cells for producing "Factor H". Conversely, this means that it would have been difficult to determine the base sequence encoding mouse IL-18/IGIF unless the mouse cells which produce IL-18/IGIF were first identified.

It should be also be emphasized that Timmann used an antibody against "Factor H" to isolate "Factor H" from human serum, as is evident from the following description in Timmann at page 1265, second column:

> MATERIALS AND METHODS
>
> Complement components and antiserum. The human complement components C3(17), factor B(18), D(19), and H(20) were purified as described previously. Isolated factor I and a goat anti-serum to human factor H were generously provided by Dr. Hans J. Muller-Emberhard from this institute. (Emphasis added)

Since an antibody against mouse IL-18/IGIF had not been known in prior art at the time the present application was filed, it is further evidence that the method disclosed by Timmann would not have been applicable to the isolation of mouse IL-18/IGIF.

Turning to the rejection itself, the examiner states that, while Nakamura does not teach a monoclonal antibody to the protein factor, the secondary Campbell reference is considered by the examiner to teach that it is "customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it (sometimes without a clear objective for their application)", that the potential of monoclonal antibodies in the basic research is considerable, and that in principle they can resolve a single protein from a complex mixture or indeed a single epitope responsible for a

specific function of a complex macromolecule. Based upon this teaching, the examiner alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to make the antibodies specific to Nakamura's protein factor inducing IFN-gamma production because it is desirable and conventional in the art, following the discovery of a new protein, to both clone the genes coding for it and make monoclonal antibodies to it, as indicated by Campbell.

As argued in our previous responses and as stated by Dr. Okamura in his declaration, Nakamura did not succeed in isolating mouse IL-18/IGIF, and it would not have been obvious to one of ordinary skill in the art at the time the invention was made to make the claimed antibody since Nakamura did not succeed in isolating mouse IL-18/IGIF.

As Campbell states, it may be "customary now for any group working on a macromolecule to both clone the genes coding for it and make monoclonal antibodies to it". However, obtaining mRNA from "macromolecule" producing cells is indispensable for cloning the target gene encoding the macromolecule. Furthermore, obtaining the "macromolecule" as antigen with relatively high purity and in relatively large amounts is also indispensable for preparing monoclonal antibodies to the "macromolecule". In this regard, Nakamura did not obtain either mouse IL-18/IGIF producing

cells or mouse IL-18/IGIF with relatively high purity and in a relatively large amount. Nakamura states at page 69, first column, second paragraph:

> The cells producing the factor have also not been identified. In order to get enough factor for a detailed analysis of its molecular characteristics, this problem of identification should be solved.

It is abundantly clear from this disclosure that Nakamura was unable to identify the cells producing Nakamura's factor. Applicants therefore believe that it would have been difficult for a person of ordinary skill in the art at the time the presently claimed invention was made to prepare mouse IL-18/IGIF by recombinant DNA techniques because the cells from which to prepare the mRNA encoding the macromolecule had not even been identified.

At page 6 of the Office Action, the examiner alleges that applicant's argument at pages 7-8 of the response is not persuasive, referring to the following statements in Dr. Okamura's declaration:

> (a) the serum factor whose apparent molecular mass was previously found to be 75 kDa by gel filtration was shown to contain the same 18- to 19-kDa IGIF
>
> (b) the protein species with a molecular weight of 75 to 80 kDa was reduced to 19 kDa on 0.1% SDS-polyacrylamide gels in the presence of DTT

However, it should be pointed out that the findings (a) and (b) are not those obtained by Nakamura using Nakamura's factor, but rather are those obtained by Dr. Okamura using samples newly prepared by Dr. Okamura. Please see the following statement at page 4, lines 17-22 of the declaration:

> we *re-prepared* Nakamura's factor for comparison with IGIF. The *re-prepared* factor exhibited an IFN-γ-inducing activity in a protein species with a molecular weight of 19 kDa in addition to the one with a molecular weight of 75 to 80 kDa by molecular sieving in the presence of dithiothreitol (DTT). (emphasis added)

If Nakamura's factor prepared by Nakamura in the applied Nakamura reference is the same as in the samples prepared by Okamura in the declaration, then the same results should have been obtained, but they were not.

Moreover, even though Nakamura's factor is considered to comprise mouse IL-18/IGIF, it is not certain whether Nakamura's factor is an oligomer of mouse IL-18/IGIF or a complex of mouse IL-18/IGIF and other proteins bound thereto. The examiner, however, takes the position that Nakamura's factor is an oligomer of mouse IL-18/IGIF, without any clear evidence or reasonable grounds to substantiate such a position.

Apart from Dr. Okamura's declaration, the examiner states that monoclonal antibodies made to Nakamura's factor of 75kDa *would bind* to the later identified factor of 19kDa as they consist of the same molecule. This statement is unsubstantied by any evidence whatsoever. Okamura et al., *Infection and Immunity*, 63(10):3966-3972 (1995), merely states:

> Thus, IGIF in the serum sample was proved to be the same IGIF as that found in the liver extract, and it was considered to be bound to another protein or to exist in an oligomeric form. (see page 3969, left column, lines 22-25)

Accordingly, in the Okamura reference, which was published later than the applied Nakamura reference, it is still uncertain if the IGIF is an oligomer of mouse IL-18/IGIF or a complex of mouse IL-18/IGIF and other proteins bound thereto. It is therefore unreasonable for the examiner to conclude that "monoclonal antibodies made to Nakamura's factor of 75kDa *would bind* to the later identified factor of 19kDa as they consist of the same molecule.

Since Nakamura did not isolate mouse IL-18/IGIF and did not obtain mouse IL-18/IGIF with a sufficiently high purity and in a sufficiently large amount for preparing a monoclonal antibody to mouse IL-18/IGIF, Nakamura in combination with

Campbell would not have led one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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